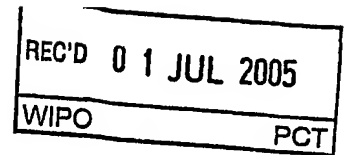


# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference 04272B88	<b>FOR FURTHER ACTION</b>		See Form PCT/PEA/416
International application No. PCT/B2004/002204	International filing date (day/month/year) 05.07.2004	Priority date (day/month/year) 18.07.2003	
International Patent Classification (IPC) or national classification and IPC C07D471/04, C07D487/04, C07K7/52, A61K38/04			
Applicant UNIVERSITA' DEGLI STUDI DI MILANO ET AL.			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p style="margin-left: 20px;">a. <input type="checkbox"/> sent to the applicant and to the International Bureau) a total of sheets, as follows:</p> <p style="margin-left: 40px;"><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p style="margin-left: 40px;"><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p style="margin-left: 20px;">b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>			
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input checked="" type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>			
Date of submission of the demand  04.02.2005		Date of completion of this report  30.06.2005	
Name and mailing address of the international preliminary examining authority:  <div style="display: inline-block; vertical-align: middle;"> European Patent Office  D-80298 Munich  Tel. +49 89 2399 - 0 Tx: 523656 epmu d  Fax: +49 89 2399 - 4465 </div>		Authorized Officer  Telephone No. +49 89 2399-8556 Samsam Bakhtiary, M.	



**INTERNATIONAL PRELIMINARY REPORT  
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International application No.  
PCT/IB2004/002204

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**Box No. I Basis of the report**

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1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
  - ☐ publication of the international application (under Rule 12.4)
  - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements\*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

**Description, Pages**

1-32 as originally filed

**Claims, Numbers**

1-36 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing *(specify)*:
  - ☐ any table(s) related to sequence listing *(specify)*:
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing *(specify)*:
  - ☐ any table(s) related to sequence listing *(specify)*:

\* If item 4 applies, some or all of these sheets may be marked "superseded."

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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	5,7,8,12,13,20,21
	No: Claims	1-4,6,9,10,11,14-19,22-36
Inventive step (IS)	Yes: Claims	
	No: Claims	1-36
Industrial applicability (IA)	Yes: Claims	1-36
	No: Claims	

2. Citations and explanations (Rule 70.7):

**see separate sheet**

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**Box No. VII Certain defects in the international application**

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The following defects in the form or contents of the international application have been noted:

**see separate sheet**

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Reference is made to the following documents:

- D1: BELVISI, LAURA ET AL: "Cyclic RGD peptides containing azabicycloalkane reverse-turn mimics" HELVETICA CHIMICA ACTA , 85(12), 4353-4368 CODEN: HCACAV; ISSN: 0018-019X, 2002, XP002300144
- D2: GENNARI CESARE ET AL: "Solid-phase synthesis of peptides containing reverse-turn mimetic bicyclic lactams" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, no. 2, 1999, pages 379-388, XP002180752 ISSN: 0223-5234
- D3: WO 97/05160 A (PALEARI FABIO ; CRISCUOLI MARCO (IT); SALIMBENI ALDO (IT); MENARINI FA) 13 February 1997 (1997-02-13)
- D4: WO 96/30396 A (KAHN MICHAEL ; MOLECUMETICS LTD (US)) 3 October 1996 (1996-10-03)
- D5: BELVISI LAURA ET AL: "Conformational preferences of peptides containing reverse-turn mimetic bicyclic lactams. Inverse.gamma.-turns versus type-II'.beta.-turns. Insights into.beta.-hairpin stability" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, no. 2, 1999, pages 389-400, XP002180753 ISSN: 0223-5234
- D6: COLOMBO L ET AL: "Synthesis of new bicyclic lactam peptidomimetics by ring-closing metathesis reactions" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 59, no. 25, 16 June 2003 (2003-06-16), pages 4501-4513, XP001183922 ISSN: 0040-4020
- D7: COLOMBO L ET AL: "Stereoselective synthesis of 6,5-bicyclic reverse-turn peptidomimetics" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 54, no. 20, 14 May 1998 (1998-05-14), pages 5325-5336, XP004116433 ISSN: 0040-4020
- D8: BOATMAN P DOUGLAS ET AL: "Secondary Structure Peptide Mimetics: Design, Synthesis, and Evaluation of.beta.-Strand Mimetic Thrombin Inhibitors" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 42, no. 8, 1999, pages 1367-1375, XP002180751 ISSN: 0022-2623

D9: COLOMBO L ET AL: "Conformationally Constrained Dipeptides: Synthesis of 7,5- and 6,5-Fused Bicyclic Lactams by Stereoselective Radical Cyclizations" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 36, no. 4, 23 January 1995 (1995-01-23), pages 625-628, XP004028813 ISSN: 0040-4039

D10:EP-A-1 077 218 (SIGMA TAU IND FARMACEUTI) 21 February 2001 (2001-02-21)

## **2. Novelty**

The claimed subject matter is concerned heterocyclic intermediates (claims 1-13), peptido-mimetic compounds, process to make it and its use (claims 16-36), use of heterocyclic intermediates to make peptido-mimetic compounds (claims 14-15).

### **2.1 heterocyclic intermediate and its use (claims 1-15)**

Documents D1-D9 (see search report cited parts) anticipate the subject matter of claims 1-4,6,9-11,14,15 of this application.

The remaining subject matter when R3 is allyl, hydroxypropyl, hydroxyethyl and alkyl can be considered as novel.

### **2.2 peptido-mimetic compounds and use (claims 16-36)**

Documents D1 (see p.4355, compound 1) and D2 (p.380, compounds 14b, 15b) anticipate the 16-19,22-36.

## **3. Inventive step**

Document D1, which is considered to represent the most relevant state of the art, discloses (cf. see whole document and compound 1 on page 4355) a compound from which the subject-matter of claims 20 and 21 differs in that the substituent on position 3 of the azabicycloalkane is allyl, hydroxyethyl or hydroxypropyl instead of benzyl.

The problem to be solved by the present invention may therefore be regarded as to provide novel derivatives useful as inhibitors for angiogenesis.

The solution proposed in claims 20 and 21 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

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The skilled person knows from the teachings of D10 (no substituent on position 3) and of D1 that a substituent on position 3 of the azabicycloalkane does not influence the biological activity of the molecule, so the skilled man would expect that the compounds of subject matter of claims 20 and 21 to exert biological properties.

Concerning the intermediates to make the end product of claims 20 and 21, these cannot be considered as inventive since the end product themselves do not involve inventive step.

**Re Item VII**

**Certain defects in the international application**

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D9 is not mentioned in the description, nor are these documents identified therein.

**Re Item VIII**

**Certain observations on the international application**

In claim 1, the terms "substituted", "lower", "suitable protective group" should be defined. The same goes for claim 16.